UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: March 6, 1978

SUBJECT: Request for 1) a temporary tolerance for O-ethyl O-(2-isopropoxy-carbonyl)phenyl isopropylphosphoramidothioate and its cholinesterase inhibiting metabolites in or on corn grain at 0.1 ppm; 2) an exemption from a tolerance for eggs, meat, fat and meat by-products of cattle, goats, hogs, horses, poultry and sheep, and milk; 3) EUP for Oftanol 15% Granular; 4) EUP for Oftanol 20% Granular; and 5) EUP for Oftanol 6 Emulsifiable.

FROM: William B. Greear
Toxicology Branch, RD (WH-567) for

TO: Donald Stubbs
Special Registration Section, RD

Pesticide Petition No. 8G2025

Caswell No. 447AB

Mobay Chemical Corp.
Chemagro Agri. Div.
Kansas City, Missouri

Recommendations

1. The submitted toxicity data will toxicologically support the temporary tolerance of 0.1 ppm in or on corn; however, TOX defers to CB the question as to the appropriateness of the exemption request. In addition, the question must be raised as to the disposition of the corn forage and whether or not finite residues are likely to occur.

2. Prior to the establishment of permanent tolerances the following information and additional studies will be required:

a. Subchronic Study in Rats - Reports #37381 and 37382

The number of the animals reported to have died prematurely does not match in the two reports. Explain the discrepancy.

b. Teratology Study in Rats - Report #35482

Identify the "slight bone alterations" observed in the study. Historical data on the incidence of anomalies and malformations in this strain should be submitted.

c. Teratology Study in Rabbits/Rats - Report #46931

Historical data on the incidence of anomalies and malformations in this strain must be submitted in order to properly evaluate the data.

d. Chronic Feeding Study in a Rodent Species

e. Oncogenic Studies in Two Species

f. Subchronic Feeding Study in Dogs (6 months)

3. The submitted toxicity data generated on Oftanol 6 Emulsifiable and Oftanol 15% are adequate; however, the following changes in precautionary labeling are recommended:

a. Oftanol 6 Emulsifiable

-change "Poisonous if swallowed, inhaled or absorbed through the skin" to read "Fatal if swallowed, inhaled or absorbed through the skin"

-delete "Information as to suitable types of masks or respirators is available from the U.S. Bureau of Mines"

-change "Do not get in eyes or on skin" to read "Do not get in eyes, on skin or on clothing "

-add "Call a physician" immediately following the statement "If eyes are contaminated, wash with flowing water for at least 15 minutes"

b. Oftanol 15% Granular and 20% Granular*

-delete "Information as to suitable types of masks or respirators is available from the U.S. Bureau of Mines"

-change "Do not get in eyes or on skin" to read "Do not get in eyes, on skin or on clothing."

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* At the time registration is sought acute toxicity data on Oftanol 20% Granular will be required.

-add "Call a physician" immediately following the statement "If eyes are contaminated, wash with flowing water for at least 15 minutes"

Residue Chemistry Considerations

Note: This review contains confidential information.

A. Substance Identification

1. Chemical Name: O-ethyl O-(2-isopropoxycarbonyl)phenyl isopropylphosphoramidothioate

2. Synonyms: Oftanol, Isofenphos, Fenisophos, Bay 92114, SRA 12869, 1-methylethyl 2-[[ethoxy[(1-methylethyl) amino]phosphinothioyl]oxy]benzoate

3. Purity of Technical Material and Structure:

(see attachment #1)

4. Physical/Chemical Data:

a. Form/Color: yellow-brown liquid
b. Odor: like sulfur
c. Molecular Weight: 345
d. Specific Gravity: 1.135 @ 20°C
e. Boiling Point: decomposition @ 220°C
f. Melting Point: <-25°C
g. Vapor Pressure: 4×10^{-6} millibar @ 20°C
5×10^{-5} millibar @ 40°C
h. Solubility: soluble in xylene, cyclohexanone, isopropanol and methylene chloride - >60g/100g solvent; soluble in water - 2.38 mg/ml water
i. Chemical Class: organophosphorous compound - an irreversible inhibitor of acetylcholinesterase.

B. Referenced Petitions

N/A

C. Formulations

1. Oftanol 15% Granular

Active Ingredient	%
Oftanol Technical (90%a.i.)	17.2
Inert Ingredients*	
[redacted]	
	100.0

2. Oftanol 20% Granular

Active Ingredient	%
Oftanol Technical (90% a.i.)	23.0
Inert Ingredients*	
[redacted]	
	100.0

3. Oftanol 6 Emulsifiable

Active Ingredient	%
Oftanol Technical (90% a.i.)	75.3
Inert Ingredients*	
[redacted]	
	100.0

* Inerts are cleared under 180.1001(c) and (d)

D. Uses Proposed - Insecticide

(see attachment #2 - labeling)

Review

A. Toxicology, Pharmacology and Metabolism Studies

1. Prior Studies - N/A

2. Summary Tables of Newly Submitted Toxicity Studies

(see attachment #3)

3. SRA 12869 Acute Toxicological Studies - (Bayer AG-Institut Für Toxikologie, Report #34162, 5/15/72, Acc #096659)

a. Oral LD_{50} in Male Rats

120 Wistar II rats, weighing 160-220g, were divided into 8 groups of 15 animals each and administered 2.5, 5.0, 10, 25, 30, 40, 50 and 60 mg/kg of the test material, dissolved in Lutrol, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 38.7 (34.3 - 43.7) mg/kg slope = 1.2
Toxic Signs: signs typical of ChE inhibition
TOX Category: I
Classification: Core-Minimum Data
1) necropsies were not performed.

b. Oral LD_{50} in Female Rats

150 Wistar II rats, weighing 160-220g, were divided into 10 groups of 15 animals each and administered 2.5, 5, 10, 20, 25, 30, 35 and 40 mg/kg of the test material, dissolved in Lutrol, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 28.0 (25.3 - 30.9) mg/kg slope = 1.3
Toxic Signs: signs typical of ChE inhibition
TOX Category: I
Classification: Core-Minimum Data
1) necropsies were not performed.

c. Oral LD_{50} in Female Mice

150 NMRI mice, weighing 18-22g, were divided into 10 groups of 15 animals each and administered 5, 10, 25, 50, 75, 80, 90, 100, 125 and 150 mg/kg of the test material, dissolved in Lutrol, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 91.3 (84.9-98.2)mg/kg slope = 1.19
Toxic Signs: signs typical of ChE inhibition
TOX Category: II
Classification: Core-Minimum Data
1) necropsies were not performed.

d. Oral LD_{50} in Male Mice

150 NMRI mice, weighing 18-22g, were divided into 10 groups of 15 animals each and administered 5, 10, 25, 50, 75, 100, 125, 150, 175 and 200 mg/kg of the test material, dissolved in Lutrol, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 127 (113-143)mg/kg slope = 1.3
Toxic Signs: signs typical of ChE inhibition
TOX Category: Core- Minimum Data
1)necropsies were not performed.

e. Oral LD_{50} in Female Rabbits

15 rabbits, weighing 2.5-3.5kg, were divided into 5 groups of 3 animals each and administered 25, 50, 100, 200 and 350 mg/kg of the test material, dissolved in Lutrol, by gavage. The animals were observed for 14 days.

Results

$LD_{50} \approx 150$ mg/kg
Toxic Signs: signs typical of ChE inhibition
TOX Category: II
Classification: Supplementary Data
1) too few animals/dose level were tested.

f. Oral Toxicity in Female Dogs

Four beagles, weighing 10-11 kg, were divided into 2 groups of 2 animals each and administered 10 or 25 mg/kg of the test material, dissolved in Lutrol, by gavage. The animals were observed for 14 days.

Results

$LD_{50} > 25$ mg/kg (no mortalities occurred)

Toxic Signs: signs typical of ChE inhibition
TOX Category: N/A
Classification: Supplementary Data
1) the LD_{50} value was not determined.

g. Intraperitoneal Administration in Male Rats

150 Wistar II rats, weighing 160-220g, were divided into 10 groups of 15 animals each and administered 0.25, 0.5, 1.0, 2.5, 5, 10, 25, 37.5, 50 and 75 mg/kg of the test material, dissolved in Lutrol, by i.p. injection. The animals were observed for 14 days.

Results

LD_{50} = 35.8 (29.1-44.1) mg/kg slope = 1.3

Toxic Signs: signs typical of ChE inhibition
Classification: Core

h. Intraperitoneal Administration in Female Rats

210 Wistar II rats, weighing 160-220g, were divided into 14 groups of 15 animals each and administered 0.25, 0.5, 1, 2.5, 5, 10, 17.5, 20, 22.5, 25, 30, 37.5, 50 and 100 mg/kg of the test material, dissolved in Lutrol, by i.p. injection. The animals were observed for 14 days.

Results

LD_{50} = 29.5 (27.0-32.2)mg/kg slope = 1.2

Toxic Signs: signs typical of ChE Inhibition
Classification: Core

i. 4-Hr. Dermal LD_{50} in Male Rats

30 Wistar II rats, weighing 160-220g, were divided into 3 groups of 10 animals each and received dermal applications of 500, 750 and 1000 µl of the test material, dissolved in Lutrol, to the clipped skin of their backs. Following a 4-hr exposure period, the test material was washed off the skin. Observations were made for 14 days.

Results

LD_{50} > 1000 µl/kg

TOX Category: N/A
Classification: Supplementary Data
1) the exposure period was 1/6 of that which is normally required.

j. 7-Day Dermal Contact in Rats

40 Wistar II rats, weighing 160-220g, were divided into 4 groups of 10 animals each and received dermal applications of 100, 150, 200 and 250 µl/kg of the test material, dissolved in Lutrol, to the clipped skin of their backs. The test material was allowed to remain in contact with the skin for 7 days. The animals were observed for 14 days.

Results

LD_{50} = 188 (160-221) µl/kg slope = 1.4

TOX Category: I
Classification: Core-Minimum Data
1) necropsies were not performed.

k. 4-Hr. Inhalation LC_{50} in Male Rats

24 Wistar II rats, weighing 160-220g, were divided into 6 groups of 4 animals each and exposed to analytical concentrations of .026, .122, .185, .231 and .270 mg/L of the test material for a 4 hour period. In addition, 2 groups of 4 rats each were exposed to .029 and .055 mg/L of the test material for a period of 4 hours per day for 5 days. The animals were observed for 14 days.

Results

LC_{50} (4-hr exposure) = 0.21 mg/L

LC_{50} (5x4-hr exposure) >0.055 mg/L

TOX Category: II
Classification: Core-Minimum Data (acute exposure);
Supplementary Data (subchronic exposure)
1) necropsies were not performed; too few parameters were measured in the subchronic exposure.

l. 4-Hr. Inhalation LC_{50} in Female Rats

28 Wistar II rats, weighing 160-220g, were divided into 7 groups of 4 animals each and exposed to analytical concentrations of .025, .062, .090, .136, .167, .199 and .249 mg/L of the test material for a period of 4 hours. In addition, two groups of 4 rats each were exposed to .029 and .055 mg/L of the test material for a period of 4 hours per day for 5 days. The animals were observed for 14 days.

Results

LC_{50} (4-hr exposure) = 0.144 mg/L

LC_{50} (5x4-hr exposure) is between .029 and .055 mg/L

TOX Category: II
Classification: Core-Minimum Data (acute exposure);
Supplementary Data (subchronic exposure)
1) necropsies were not performed; too few parameters were measured in the subchronic exposure.

m. 4-Hr. Inhalation LC_{50} in Male Mice

20 NMRI mice, weighing 18-22g, were divided into 5 groups of 4 animals each and exposed to analytical concentrations of .032, .073, .144, .201 and .272 mg/L of the test material for a 4-hr period. The animals were observed for 14 days.

Results

$LC_{50} > 0.272$ mg/L

TOX Category: II
Classification: Core-Minimum Data
1) necropsies were not performed.

n. 4-Hr. Inhalation LC_{50} in Male Hamsters

20 golden hamsters, weighing 80-100g, were divided into 5 groups of 4 animals each and exposed to analytical concentrations of .032, .073, .144, .201 and .272 mg/L of the test material for a period of 4 hours. The animals were observed for 14 days.

Results

$LC_{50} = 0.23$ mg/L

TOX Category: II
Classification: Core-Minimum Data
1) necropsies were not performed.

o. Static Spray Inhalation Study

SRA 12869, dissolved in a mixture of alcohol and Lutrol (1:1), was sprayed at 30-minute intervals during the 4 hour exposure period, into 2 M^3 chambers containing the experimental animals. Each group contained 2 rabbits, 5 hamsters, 10 rats and 20 mice. The 3 groups were exposed to analytical concentrations of .014, .043 and .172 mg/L of the test material. The animals were kept under observation for 14 days.

Results

The relative sensitivity of the different species are as follows:

rats > hamsters > mice > rabbits

Classification: Supplementary Data

p. Dermal Irritation

0.5 ml of the test material was applied to one intact and one abraded skin site on the clipped back of each of 6 albino rabbits. Dermal irritation was scored at 24 and 72 hours, according to Draize.

Results

P.I. = .21/8.00
TOX Category: IV
Classification: Core-Minimum Data
1) readings were not made on 2 intact and 2 abraded skin sites.

q. Eye Irritation Study

0.1 ml of the test material was instilled into the conjunctival sac of one eye of each of 6 albino rabbits. The eyes were examined at 24, 48 and 72 hours. The eyes were scored according to the FHSLA.

Results

The test material was "negative" for eye irritation by FHSLA criteria.

TOX Category: can not be determined
Classification: Supplementary Data
1) although the scores were reported as "negative" this does not imply that no discernable irritation was observed. Scoring should be performed according to Draize, i.e. numerical values for eye irritation should be recorded for each animal.

4. Acute Dermal Toxicity of Oftanol Technical - (Chemagro R&D, Report #53774, 9/30/77, Acc #096659)

40 New Zealand white rabbits, were divided into 5 groups of 4 male and 4 female animals each and received dermal applications of 54, 105, 206, 405 and 793 mg/kg of the test material to the clipped and abraded skin of their backs. The test material was applied under an occlusive wrapping. After 24 hours the wrappings were removed and the backs wipped clean. Observations were made for 14 days. Necropsies were performed.

Results

LD_{50} (male) = 162 (80-328) mg/kg

LD_{50} (female) = 315 (156-635) mg/kg

Toxic Signs: ataxia, lethargy, muscular fasciculation, diarrhea, salivation

Necropsy: distended gall baldders and pale livers

TOX Category: I

Classification: Core- Minimum Data

1) food consumption and body weights were not recorded daily.

5. SRA 12869 Acute Neurotoxicity Studies in Hens - (Bayer AG - Institut Für Toxicologie, Report #34025, 3/20/72; and Huntingdon Research Centre, Report #53881, 7/19/72, Acc #096657)

The test material was dissolved in Lutrol and administered to white Leghorn hens, weighing 1.4-1.9 kg, by gavage or by intraperitoneal injection. The observation period was 6 weeks. Five hens which survived an oral dose of 20 mg SRA 12869/Kg, six atropinized hens dosed with 74 mg SRA 12869/kg and five positive control hens which had received 350 mg TOCP/kg by the oral route were narcotized with pentobarbital 3 weeks after administration of the test compound and then sacrificed. The brain, spinal marrow and sciatic nerve were prepared for histological examination.

Test #1: Oral Toxicity

Single doses of SRA 12869 were orally administered to hens, according to the following schedule:

Dose (mg/kg)	10	15	20	25	40
No. of Animals	1	10	10*	10	2

*Hens sacrificed at 3 weeks

Results

LD_{50} = 20.9 (17.6-24.9) mg/kg slope = 1.4

Toxic Signs: depression (absent by day 5); no signs of neurotoxicity were observed.

Classification: Core-Minimum Data
1) a 2nd dose was not administered.

Test #2: Intraperitoneal Toxicity

Single doses of SRA 12869 were administered by i.p. injection to hens, according to the following schedule:

Dose (mg/kg)	7.5	10	12.5	15	17.5	20
No. of Animals	10	10	10	10	10	2

Results

LD_{50} = 11.4 (9.4-13.9) mg/kg slope = 1.37
Toxic Signs: no signs of neurotoxicity were observed
Classification: Supplementary Data
1) nervous tissue was not examined microscopically.

Test #3: Oral Toxicity Following Pretreatment with Atropine & PAM

Hens were pretreated with 50 mg atropine sulfate/kg and 100 mg PAM/kg (injected i.p.). The hens were then orally administered single doses of SRA 12869 according to the following schedule:

Dose (mg/kg)	45	50	100
No. of Animals	12	6	2

Results

Pretreatment of the hens with atropine and 2 PAM had a marked protective effect (LD_{50} > 45 mg/kg). No signs of neurotoxicity were observed.

Classification: Supplementary Data
1) nervous tissue was not examined microscopically.

Test #4: Oral Toxicity to Atropinized Hens

Hens were pretreated with 50 mg atropine sulfate/kg (injected i.p.). The hens were then orally administered single doses of SRA 12869 according to the following schedule:

Dose (mg/kg)	35	40	50	70	74	75	100
No. of Animals	10	10	10	10*	10	10	10

*Hens sacrificed at 3 weeks.

Results

LD_{50} = 74 (60-91) mg/kg
Toxic Signs: no signs of neurotoxicity were observed.
Classification: Core-Minimum Data
1) a 2nd dose was not administered.

Test #4: Oral Administration of TOCP

Five hens were administered 350 mg TOCP/kg. The hens were observed for 3 weeks.

Results

Signs indicative of neurotoxicity were observed.

Classification: Core-Minimum Data
1) this study is considered to be an integral part of the other neurotoxicity studies.

6. Subacute Toxicity Studies - (Bayer AG-Institut Für Toxikologie, Report #34098, 5/15/72, Acc #096657)

a. Subacute Oral

120 Wistar II rats, with an average weight of 161g (male) and 153g (female), were divided into 4 groups of 15 male and 15 female rats each and administered 0.1, 0.25 and 2.5 mg/kg of SRA 12869 by gavage, daily, for a period of 30 days. A concurrent control group of 15 male and 15 female rats received 5.0 ml Lutrol/kg. The animals were observed daily for abnormal behavioral reactions and mortality. Plasma and erythrocyte cholinesterase activity were determined on days 0, 9, 16 and 30. SGOT, SGPT and LDH activity were determined only in the control and high dose male rats at the end of the study. At the end of the study the animals were sacrificed and necropsied. The liver, kidney and adrenal weights were determined.

Results

The control and test groups were comparable with respect to appearance, body weight gain and relative organ weights. SGOT, SGPT and LDH activities were within the normal range in male control and high dose animals. Plasma and erythrocyte cholinesterase inhibition was present in the two highest dose level groups. The necropsy examination was unremarkable.

NEL (Plasma ChE) = 0.25 mg/kg/day; LEL = 1.0 mg/kg/day
NEL (RBC ChE) = 0.25 mg/kg/day; LEL = 1.0 mg/kg/day

Classification: Supplementary Data
1) the data were summarized; too few parameters were measured.

b. Subacute Inhalation

40 Wistar II rats, with an average weight of 161g (male) and 153g (female), were divided into 2 groups of 10 male and 10 female rats each and exposed for 6 hours a day for 5 consecutive days per week over a 3-week period (15 exposures) to 0.72 and 2.93 mg/M^3 of SRA 12869. A control group of 10 male and 10 female rats was exposed to the solvent mixture of alcohol and Lutrol (1:1) at a concentration of 5000 mg/M^3. The animals were observed daily for abnormal behavioral reactions and toxic signs. Body weights were determined weekly. The following parameters were determined at the end of the study.

Hematology

RBC	MCH	MCV
Hb	WBC	Thrombocytes
PCV		

Clinical Chemistry

SGOT	SGPT	SDH
Urea	Creatinine	

Plasma and erythrocyte cholinesterase activities were determined weekly. At the end of the study the animals were sacrificed and necropsied. The following organs were weighed.

Thyroids	Heart	Spleen
Liver	Kidneys	Lungs
Adrenals	Gonads	

Results

The animals in the test and control groups were comparable with respect to appearance, body weight gain and relative organ weights. Hematologic and clinical chemistry values did not indicate any compound related effects. Plasma and erythrocyte cholinesterase inhibition was observed in animals of the high dose test group. The necropsy examination was unremarkable.

NEL = 0.72 mg/M^3; LEL = 2.73 mg/M^3 (cholinesterase inhibition)

Classification: Supplementary Data
1) the data were summarized; histopathology data were absent.

7. Special Toxicological Studies on SRA 12869 - (Bayer AG-Institut Für Toxikologie, Report #34160, 5/15/72, Acc #096657)

a. In Vitro Cholinesterase Assay

Serum, erythrocyte and brain cholinesterase activity in male SPF rats, was measured manometrically using a Warburg apparatus.

Results

I_{50} (serum) = 8.2×10^{-4} mole
I_{50} (RBC) = 3.1×10^{-4} mole
I_{50} (brain) = 2.87×10^{-4} mole

Classification: Supplementary Data

b. Cholinesterase Depression Following a Single Oral Administration

25 male Wistar II rats, weighing 170-210g, were divided into 5 groups of 5 animals each and were orally administered 0.5, 2.5, 11.5, 30.0 and 35.0 mg/kg of SRA 12869. 10 female rats were distributed into 2 groups of 5 animals each and administered 0.5 and 2.5 mg/kg of SRA 12869. Plasma and erythrocyte cholinesterase activity was measured at 2 hrs, 24 hrs, 3 days,

and 7 days. In addition, 15 male rats were divided into 3 equal groups and administered 1.0 2.5 and 3.0 mg/kg. Brain cholinesterase activity was measured 24 hours after administration.

Results

The highest level of plasma and erythrocyte cholinesterase inhibition was recorded at 2 hours. Cholinesterase inhibition was greater in erythrocytes than in plasma. No inhibition was observed at 0.5 mg/kg. Brain cholinesterase was inhibited 0, 23 and 74% at the 1.0, 2,5 and 3.0 mg/kg dose levels.

Classification: Supplementary Data

c. Antidotal Study

Male rats were administered SRA 12869 by gavage. Before the appearance of severe poisoning symptoms, the rats received an i.p. injection of 50 mg/kg atropine sulfate, 50 mg/kg 2-PAM, 20 mg/kg Toxogonin or a combination as indicated below.

Results

Dose (mg/kg) of SRA 12869	Without Antidote	With Atropine Sulfate	With PAM	With Toxogonin	With Atropine Sul.&PAM	With Atro. Sulfate & Toxogonin
35	1/15*	2/15	1/15	1/15	1/15	1/15
45	6/15	8/15	-	-	5/15	-
50	13/15	9/15	8/15	8/15	8/15	6/15
55	14/15	12/15	-	-	12/15	-
60	15/15	15/15	13/15	12/15	15/15	-
75	-	-	15/15	15/15	-	14/15
LD_{50}	44.0	45.5	48.2	49.2	47.8	52.0

Thus the antidotes had only a very slight effect
*deaths/number of animals dosed

Classification: Core Data

d. Synergism Study with Malathion and EPN

The oral toxicity of SRA 12869, malathion and EPN to male rats were determined.

LD_{50} SRA 12869 = 95.9 mg/kg
LD_{50} Malathion = 1421 mg/kg
LD_{50} EPN = 44.5 mg/kg

Next, equitoxic amounts of the pesticides were given to male rats as indicated in the table below:

SRA 12869 + Malathion (mg/kg)	No. of Animals per Treatment Group	SRA 12869 + EPN
150	15	30
200	15	40
250	15	50
300	15	60

Results

LD_{50} (SRA 12869 + Malathion) = 217 mg/kg
LD_{50} (SRA 12869 + EPN) = 44.1 mg/kg

Combined administration of SRA 12869 and malathion produced potentiation. Combination of SRA 12869 and EPN produced an additive effect.

Classification: Core

8. Studies for Embryotoxic and Teratogenic Effects on Rats Following Oral Administration - (Bayer AG-Institut Für Toxikologie, Report #35482, 10/25/77, Acc #096657)

Groups consisting of 20 to 21 fertilized female FB 30 rats, weighing 200-250g, received daily oral doses of 0, 0.3, 1.0 or 3.0 mg/kg of SRA 12869 in 5 ml of Lutrol/kg, applied by gavage, from the 6th to the 15th day of gestation. The dams were observed for signs of toxicity and body weight gains were recorded from the 6th to the 15th day of gestation. On the 20th day of gestation, the fetuses were removed from the dams by caesarian section. The fetuses were examined for external visceral malformations using the Wilson technique and for skeletal malformations by staining of the bones with Alizarin Red S. The number of implantation sites, resorptions, fetuses, stunted fetuses and average fetal and placetal weights were recorded.

Statistical methods of analysis were employed which includes the following:

a) Non-parametric ranking method described by Wilcoxon for weight gains, implantation quota, number of fetuses, resorption quota, fetal and placental weights.

b) Chi-square test for quotas of fertilized and pregnant females, number of fetuses with bone alterations, number of stunted fetuses and the malformation rate.

Results

One female died in each of the medium and high dose groups; however, the deaths were not attributed to administration of the test compound. The average number of implantation sites and fetuses per dam were comparable between control and test animals. Dams in the 3 mg/kg/day group exhibited a slightly greater resorption rate when compared to control dams; however, numerically the difference was not statistically significant. The average fetal and placental weights were comparable in all groups. The average number of stunted fetuses in the test groups did not significantly differ from that observed in the control group. No internal malformations were observed; however, the following skeletal malformations were observed:

Dose (mg/kg/day)	Finding
0	No malformation
0.3	1 fetus with wavy deformation of ribs
1.0	1 fetus with wavy deformation of ribs
3.0	1 fetus with forked ribs

In the evaluation it was stated that "the nature and frequency of the observed malformations were within the normal limits for the employed rat strain."

NEL = 3 mg/kg/day for teratogenicity

Classification: Core-Minimum Data (provisional)

1) although no maternal toxic effects were observed, the dose levels used were sufficiently high ($\approx$1/10 LD_{50}). The "slight bone alterations" should be identified. The background incidence of anomalies and malformations in this strain should be submitted.

9. Subchronic Toxicity Study on Rats - (Bayer AG-Institut Für Toxikologie, Report #37381, 3/23/73; and Huntingdon Research Centre, Report #37382, 3/27/72, Acc #096657)

150 Wistar rats, having average weights of 59.0g (male) and 62.5g (female), were distributed into 5 groups of 15 male and 15 female animals each and administered 0.5, 1, 5, 25 and 125 ppm of SRA 12869 in the diet for 3 months. A concurrent control group of 30 males and 30 females received the diet without SRA 12869. The test animals were observed daily. Food consumption and body weight gain were determined weekly. The following parameters were determined in 5 male and 5 female animals of each group at the end of 1 and 3 months.

Hematology

RBC	WBC	Hb
Reticulocytes	Thrombocytes	PCV
MCH	MCV	Differential WBC

Clinical Chemistry

SAP	SGLP	Bilirubin
SGOT	SGLDH	Protein

Urinalysis

Urea	Creatinine	Protein
Glucose	Cholesterol	

Plasma and erythrocyte cholinesterase activity were measured in 5 male and 5 female rats of each group after 1, 4, 8 and 13 weeks using the hydroxamate method of Pilz and Eben. Brain cholinesterase activity was measured manometrically in 3 animals/sex/group at the end of the study. At sacrifice, all animals were necropsied and the following organs were weighed:

Thyroid	Heart	Liver
Thymus	Lung	Spleen
Kidneys	Adrenals	Gonads

The following tissues were fixed in 10% buffered formaldehyde solution and examined histologically.

Brain	Pituitary	Eyes
Thyroids	Thymus	Heart
Aorta	Lung	Liver

Spleen	Pancreas	Stomach
Intestine	Kidneys	Adrenals
Urinary Bladder	Testes	Epididymus
Seminal Vesicle	Prostate Gland	Ovaries
Uterus		

The non-parametric ranking test of Wilcoxon was used to statistically analyze the results.

Results

During the first 2 weeks of feeding, animals fed 125 ppm of SRA 12869 in the diet developed symptoms of cholinesterase poisoning, manifested by muscular twitching, trembling and occasional salivation. Afterwards the animals fed this dietary concentration again behaved normally. Food consumption which was calculated on the basis of animal body weight halfway through the experiment was comparable between test and control animals. Male and female animals in the highest dose group had significantly lower body weights at the end of the experiment when compared to control animals. *One death was recorded in the male highest dose group which was believed to be due to pneumonia. With the exception of cholinesterase inhibition, the hematologic, clinical chemistry and urinalysis parameters measured did not reveal any effects which could be associated with administration of SRA 12869 in the diet. Plasma, erythrocyte and brain cholinesterase activity was significantly depressed at the 25 and 125 ppm treatment levels. Neither the gross nor the microscopic histologic examination revealed any compound related effects.

NEL (plasma, erythrocyte and brain cholinesterase inhibition) = 5 ppm; LEL = 25 ppm

NEL (systemic) = 25 ppm; LEL = 125 ppm (body weight)

Classification: Invalid (Provisional)

* 1) The animal reported to have died early in the experiment, in Report #37381, does not match the number of the animal reported to have died in Report #37382. This error must be corrected prior to acceptance of the study.

10. Subchronic Toxicity Study on Dogs - (Bayer AG-Institut Für Toxikologie, Report #38132, 5/28/73; and Huntingdon Research Centre, Report #38133, 4/13/73, Acc #096657)

40 pure-bred beagles, weighing 4.3-6.8kg, were distributed into 4 groups of 4 male and 4 female animals each and administered 0, 0.3, 1.0, 10.0 and 30.0 ppm SRA 12869 in the diet for 3 months. Prior to the start of the study the animals were immunized with distemper, infectious hepatitis and leptospirosis vaccine, and treated for possible endoparasite and ectoparasite infestations. The animals were observed once per day. Body weights were determined weekly. Refused feed was weighed and recorded. Prior to initiation of the study and during the last week of feeding, the pupillary reflex, patellar reflex, flexor reflex and extensor thrust were tested. Ophthalmoscopic examinations were made intially and at the end of the experiment. The following parameters were evaluated initially, after 5 weeks, and in the 13th week of feeding.

Hematology

PCV	Hb	RBC
WBC	MCH	MCV
Thrombocyte	Reticulocyte	Differential WBC
ESR	Thromboplastin Time	

Clinical Chemistry

Glucose	SGPT	SAP
Urea	SGOT	Protein
Creatinine	Cholesterol	

Urinalysis

pH	Glucose	Protein
Blood	Bilirubin	Microscopic Exam

Erythrocyte and plasma cholinesterase activity were determined initially, and after 1, 3, 6 and 13 weeks of feeding using the hydroxamate method of Pilz and Eben. At the end of the experiment, all the animals were narcotized with Evipan, sacrificed by exsanguination, and necropsied. The following organs were weighed:

Liver	Heart	Lung
Kidneys	Spleen	Testes
Ovaries	Pancreas	Thymus

The following tissues were fixed in 10% buffered Formol and examined microscopically:

Brain	Gonads	Colon
Lung	Aorta	Diaphram
Spleen	Lymph Nodes (mandi-	Eye
Kidneys	bular, axillary,	Pituitary
Tonsils	mesenteric)	Pancreas
(those red-	Esophagus	Adrenals
dened)	Gall Bladder	Prostate Gland
Stomach	Heart	Salivary Gland
(fundus,	Liver	Uterus
pylorus)	Thyroid	Ileum
Skeletal Mus.	Jejunum	Bone Marrow
Optic Nerve	Sciatic Nerve	
Thymus		
Duodenum		
Urinary Bladder		

Results

One male dog in the 1 ppm group became ill eight days after the start of the feeding study and it was sacrificed. Death was believed to be due to distemper. No abnormal behavioral reactions were observed, with the exception of the one ill animal. Food consumption and body weight gain were comparable between control and test animals. No pathological changes were seen on the fundus oculi, cornea and lense in the eyes of the animals. The neurological examinations were normal in all animals. Hematology, clinical chemistry (with the exception of cholinesterase activity) and urinalyses data were com rable in control and test animals. Plasma cholinesterase activity was depressed in 2/4 males in the 1 ppm group and in 4/4 females in the 10 ppm group after the 3rd week on test. Erythrocyte cholinesterase activity was depressed in 2/4 males and 2/4 females in the 10 ppm group after 3 weeks on test. The gross necropsy examination was negative. No significant differences in relative organ weights were observed among control and test animals. Histological examination of the tissues revealed no differences from the normal.

Results

LD_{50} (SRA 12869) = 43.1 (38.8-47.8) mg/kg

LD_{50} (SRA 12869 + antidote) = 84.2 (67.9-104.4) mg/kg

Atropine in combination with obidoxime was effective.

Classification: Core Data

13. SRA 12869; Studies of Embryotoxic and Teratogenic Effects on Rabbits Following Oral Administration - (Bayer AG-Institut Für Toxikologie, Report #46931, 11/10/75, Acc #096657)

An unknown number of female Himalayan rabbits, weighing 2-2.5 kg were mated. The mating produced 4 groups of 13, 12, 13 and 11 pregnant does which were administered 0*, 1, 2 and 5 mg/kg of SRA 12869, respectively, from day 6 through day 18 of gestation (total of 13 does), by gavage. *Control animals received 5 ml/kg of the vehicle, a 0.5% Cremophor emulsion. Body weight gain of the does during the treatment period from day 6 through day 18 of gestation as well as throughout the gestation period were recorded. On day 29 of gestation, the fetuses were removed by caesarian section. The number of implantations, resorption sites, fetuses and stunted fetuses were recorded. After removal from the uterus, the fetuses were sexed and examined for external malformations. The fetuses were then necropsied, the abdominal and thoracic organs examined and the brains were fixed and sectioned. The fetuses were eviscerated, cleared in dilute KOH, stained with Alizarin Red S, and examined for skeletal abnormalities. The following statistical methods were used to evaluate the data:

1) Non-parametric ranking method of Wilcoxon (V test of Wilcoxon, Mann and Whitney) - for weight gains, number of implantations, number of fetuses, number of resorptions, fetal weight and placental weight.

2) Chi-square test (correction of Yates) - for numbers of fetuses with bone alterations, number of fetuses with malformations number of stunted fetuses.

3) Chi-square test (correction of Yates) or the exact test of Fisher - for the quotas of fertilized and pregnant does.

Results

Five of the does in the 5 mg/kg group developed diarrhea; three of the does died following heavy weight loss. Two of the three deaths were believed to be compound related. One death was probably due to pneumonia. One doe in the 1 mg/kg group died which was also believed to be due to pneumonia. One doe in the 2 mg/kg group aborted. Does in each test group exhibited less weight gain than the controls during the treatment period. Fertility appeared not to be affected by compound administration. There were no biologically noteworthy or statistically significant differences between the test and control groups with respect to the following parameters:

- average number of implantations
- average number of fetuses
- average number of dead and resorbed embryos and fetuses
- average fetal weight
- average placental weight
- frequency of stunted fetuses
- frequency of fetuses with slight alterations in bone development

One malformed fetus was observed in the 5 mg/kg group. The fetus had arthrogryposis of both front extremeties. It was stated that this malformation was observed in fetuses of untreated mothers relatively often and was considered to be a spontaneous malformation.

Classification: Supplementary Data

1) it is unlikely that minor skeletal anomalies would not have been observed in any of the fetuses considering the fact that the NZW strain of rabbit has an incidence of $\approx$ 5.4% skeletal anomalies other than retardation of ossification (A.K. Palmer).This must be explained. In addition the incidence of arthrogryposis in this strain of rabbit should be reported.

14. SRA 12869 Acute Toxicity Study in Rats - (Bayer AG-Institut Für Toxikologie, Report #47935, 2/11/76, Acc #096657)

60 Wistar II albino rats, weighing 170 to 190g, were distributed into 3 groups of 10 male and 10 female animals each and were exposed in a dynamic flow inhalation chamber to analytical concentrations of 0.314, 0.8376 and 1.300 mg/L of S 12869 for a period of 1 hour. The test material was aerosolized as a mixture in 1:1 ethanol/polyethylene glycol. The animals were observed for 14 days; afterwhich, they were sacrificed and necropsied.

Results

$LC_{50} > 1.3$ mg/L

Toxic Signs: signs typical of organophosphate poisoning
Necropsy: unremarkable
TOX Category: II
Classification: Core-Minimum Data
1) although the LC_{50} was not determined, the data indicate the LC_{50} to be in close proximity to 1.3 mg/L.

15. Acute Dermal Toxicity of Oftanol Technical - (Chemagro R&D, Report #53774, 9/30/77, Acc #096657)

32 New Zealand white rabbits, weighing 2.3-3.2 kg, were distributed into 4 groups of 4 male and 4 female animals each and received dermal applications of 105, 206, 405 and 793 mg/kg of SRA 12869 to the clipped skin of their backs. In addition, another 4 male rabbits received dermal applications of 54 mg/kg. The backs were wrapped in plastic. After 24 hours, the wrappings were removed and the backs were wiped dry. The animals were observed for 14 days. Necropsies were performed.

Results

LD_{50} (male) = 162 (80-328) mg/kg
LD_{50} (female) = 315 (156-635) mg/kg
Toxic Signs: ataxia, muscular fasciculation, diarrhea, salivation, lethargy
Necropsy: distended gall bladder, pale liver
TOX Category: I

Classification: Core-Minimum Data
1) food consumption and body weight data were not determined daily.

16. Acute Dermal Toxicity of Oftanol 15% Granular - (Chemagro R&D, Report #53775, 9/30/77, Acc #096657)

16 New Zealand white rabbits, weighing 2.22-2.67 kg, were distributed into 2 groups of 4 male and 4 female animals each and received dermal applications of 1000 and 2000 mg/kg of the test material to the abraded skin of their clipped backs. The test material was allowed to remain in contact with the skin for a period of 24 hours under an occlusive wrapping. The animals were observed for a period of 14 days. Necropsies were performed.

Results

LD_{50} > 2000 mg/kg (no deaths occurred)
Toxic Signs: ataxia
Necropsy: unremarkable
TOX Category: III
Classification: Core-Minimum Data
1) although the LD_{50} was not determined, the LD_{50} is clearly in excess of 2 g/kg and thus exhibits low dermal toxicity.

17. Eye and Dermal Irritancy of Oftanol 15% Granular - (Chemagro R&D, Report #53776, 9/30/77, Acc #096657)

Dermal Irritation

0.5g of the test material was applied to 1 intact and 1 abraded skin site on the clipped back of each of 6 New Zealand white rabbits. The animals were wrapped in plastic sheets. Following a 24 hour exposure period the wrappings were removed and the degree of irritation scored. Rabbits were again evaluated at 72 hours.

Results

P.I. = 0/8
TOX Category: IV
Classification: Core-Minimum Data
1) readings were not made on 2 intact and 2 abraded skin sites.

Eye Irritation

50 mg of the test material was placed into the left eye of each of 9 New Zealand white rabbits. Three of the 9 rabbits had their treated eye washed with 200 ml of water 45 sec after compound administration. The cornea, iris and palpebral conjunctivae were scored on days 1, 2, 3, 4, 7 and on days 14 and 21 if irritation was still present on day 7.

Results

Corneal opacity was seen in 1/6 rabbits with unwashed eyes on days 1 and 2. All of the rabbits exhibited minimal conjunctivitis clearing by day 7. Washing the eyes was beneficial.

TOX Category: II
Classification: Core-Guideline

18. Eye and Dermal Irritancy of Oftanol 6 Emulsifiable - (Chemagro R&D, Report # 53777, 9/30/77, Acc #096657)

Dermal Irritation

0.1 ml of the test material was applied to 1 intact and 1 abraded skin site on the clipped back of each of 6 New Zealand white rabbits. The animals were then wrapped in plastic sheets. Following a 24 hour exposure period, the wrappings were removed and the degree of irritation was scored. Rabbits were again evaluated at 72 hours.

Results

P.I. = 0/8
TOX Category: IV
Classification: Core-Minimum Data
1) readings were not made on 2 intact and 2 abraded skin sites.

Eye Irritation

0.1 ml of the test material was instilled into the left eye of each of 9 New Zealand white rabbits. Three rabbits had their treated eye washed with 200 ml of water 45 sec after compound administration. The cornea, iris and palpebral conjunctivae were scored on days 1, 2, 3, 4, 7 and on days 14 and 21 if irritation was still present on day 7.

Results

Unwashed Eyes: Corneal opacity in 6/6 rabbits, clearing by day 7; conjunctivitis was present in 2/6 rabbits, clearing by day 14.

Washed Eyes: Conjunctivitis in 3/3 rabbits, clearing by day 7.

TOX Category: II
Classification: Core-Guideline

19. The Acute Inhalation Toxicity of Oftanol 6 to Rats - (Chemagro R&D, Report #53778, Acc #096657)

80 Sprague-Dawley rats, weighing ≈207-273g, were divided into 4 groups of 10 male and 10 female animals each and exposed in a dynamic inhalation chamber to analytical concentrations of 0.987, 1.168, 1.725 and 2.590 mg/L of the test material for a period of 1 hour. The test material was aerosolized in a mixture of ethanol/Lutrol (1:1) and the droplet size determined by a 5-stage cascade impactor. The animals were weighed at 0, 7 and 14 days and signs of toxicity and mortality were recorded for the 14 day period. Necropsies were performed.

Results

LC_{50} (male) = 1.950 (1.393-2.730) mg/L
LC_{50} (female) = 1.650 mg/L
Toxic Signs: bloody tears, salivation, tremors and convulsions.
Necropsy: unremarkable
TOX Category: II
Classification: Core-Minimum Data
1) food consumption and body weights were not determined daily.

20. The Acute Inhalation Toxicity of Oftanol 15% Granular to Rats - (Chemagro R&D, Report # 53779, 9/27/77, Acc #096657)

10 male and 10 female Sprague-Dawley rats, having average weights of 334g (male) and 207g (female), were exposed in a 212.9 L exposure chamber to a nominal concentration of 20000 µg/L of the test material in the form of a dust for a period of 1 hours. The animals were suspended from the axle of the drum (exposure chamber) and the drum rotated in order to suspend the test material. The animals were observed for a period of 14 days. Necropsies were performed.

Results

LC_{50} > 20 mg/L
Toxic Signs: none
Necropsy: chronic pneumonia in 3 animals
TOX Category: IV
Classification: Core-Minimum Data
1) although only 1 dose level was employed, the level was sufficiently high to indicate that the test material is not highly toxic by the inhalatory route of exposure.

21. Acute Dermal Toxicity of Oftanol 6 Emulsifiable - (Chemagro R&D, Report #53780, 9/30/77, Acc #096657)

32 New Zealand white rabbits, weighing 2.16-3.14kg, were distributed into 4 groups of 4 male and 4 female animals each and received dermal applications of 63, 125, 250 and 500 mg/kg of the test material to the abraded skin of their clipped backs. The test material was allowed to remain in contact with the skin for a period of 24 hours under an occlusive wrapping. The animals were observed for a period of 14 days. Necropsies were performed.

Results

LD_{50} (male) = 252 (152-411) mg/kg
LD_{50} (female) = 198 (109-291) mg/kg
Toxic Signs: lethargy, diarrhea, muscular fasciculations
Necropsy: pale livers and intestinal lesions
TOX Category: II
Classification: Core-Minimum Data
1) body weights and food consumption were not determined daily.

22. The Skin Sensitizing Properties of Oftanol Technical to Guinea Pigs - (Chemagro R&D, Report #53851, 10/13/77, Acc #096657)

15 white male guinea pigs, weighing 330-415 g, were prepared by shaving their backs and flanks. The test material, which was dissolved in saline to form a 0.1% solution, was injected intradermally every other day (Mon, Wed, Fri), for a total of 10 injections. Twenty-four hours after injection, readings were made of the injection site. The challenge dose was injected 14 days after the last sensitizing injection. The animals were examined 24 hours later for signs of sensitization.

Results

The test material did not evoke a sensitization reaction.

Classification: Core-Minimum Data
1) readings were not made 48 hours after injection.

23. The Acute Oral Toxicity of Oftanol 6 Emulsifiable - (Chemagro R&D, Report #53883, 10/25/77, Acc #096657)

80 Holtzman derived Sprague-Dawley rats, weighing 188-270g, were divided into 8 groups of 10 animals each and administered the test material, diluted in polyethylene glycol, according to the following schedule:

	Dose (mg/kg)			
Male	22	32	47	69
Female	14	22	32	47

The animals were observed for a period of 14 days. Females were weighed on days 7 and 14. Necropsies were performed.

Results

LD_{50} (male) = 30 (13-72) mg/kg
LD_{50} (female) = 27 (23-32) mg/kg
Toxic Signs: diarrhea, muscular fasciculations, tremors, ataxia, lacrimation, decreased activity and rough coats.
Necropsy: congested lungs and livers
TOX Category: I
Classification: Core-Minimum Data
1) body weights and food consumption were not determined daily.

24. Ames Test for Oftanol (Isofenphos) - (Prof. Dr. F. Oesch, Report #53954; 9/29/77, Acc #096657)

Oftanol was tested in the presence and in the absence of an activating system (S-9 mix) for mutagenicity with Salmonella typhemurium TA 100, TA 1537 and TA 98. The following doses/plate were used in the presence and absence of the S-9 activating system:

	Dose (nl/plate)						
Without S-9	31.5	100	315	1000	3150		
With S-9	3.15	10	31.5	100	315	1000	3150

In the non-activation assay, N-methyl-N'-nitro-N-nitroso-guanidino and benzo (a) pyrene 4,5 oxide were used as positive controls. In the activation assay 3-methylcholanthrene, benzo (a)pyrene and 2-aminoanthracine were used as positive controls. Two negative controls were used in each of the two test systems. Following 2-3 days incubation, the number of revertant colonies per plate were scored.

Results

In both the activated and the non-activated test systems the number of revertants per plate were comparable among test and negative control plates. The increase in the number of revertants per plate on the positive control plates indicates that the two test systems were sensitive to certain chemical mutagens.

Classification: Core Data

25. The Acute Oral Toxicity of Oftanol Technical - (Chemagro R&D, Report #54000, 10/11/77, Acc #096557)

100 Sprague-Dawley rats, weighing 160-260g were divided into 10 groups of 10 animals each, and administered the test material diluted in Lutrol, by gavage, according to the following schedule:

	Dose (mg/kg)				
Male	20.6	28.9	40.5	56.6	79.3
Female	14.7	20.6	28.9	40.5	56.6

The animals were observed for a period of 14 days. Necropsies were performed.

Results

LD_{50} (male) = 45 (39-53) mg/kg

LD_{50} (female) = 32 (28-36) mg/kg

Toxic Signs: lethargy, lacrimation, diarrhea, tremors; survivors exhibited body weight gain.
Necropsy: congested livers
TOX Category: I
Classification: Core-Minimum Data
1) body weights and food consumption were not determined daily.

26. The Acute Oral Toxicity of Oftanol 15% Granular - (Chemagro R&D, Report #54003, 10/3/77, Acc #096657

100 Holtzman derived Sprague-Dawley rats, weighing 172-216g, were administered the test material, suspended in polyethylene glycol, by gavage, according to the following schedule:

	Dose (mg/kg)				
Male	102	150	220	323	475
Female	69	102	150	220	323

The animals were observed for a period of 14 days. Necropsies were performed.

Results

LD_{50} (male) = 260 (198-342) mg/kg

LD_{50} (female) = 202 (177-231) mg/kg

Toxic Signs: lethargy, diarrhea, salivation, head tremors, muscular fasciculations and rough coats

Necropsy: congested lungs

TOX Category: II

Classification: Core-Minimum Data

1) body weights and food consumption were not determined daily.

27. HOL 0654; Acute Toxicity Studies - (Bayer AG-Institut Für Toxikologie, Report #41883, 8/21/74, Acc #096657)

a. Acute Oral Toxicity

195 Wistar II albino rats, weighing 160-180g, were divided into 7 groups of 15 males each and 6 groups of 15 females each and administered the test material, diluted in a distilled water-Cremophor EL mixture, by gavage, according to the following schedule:

	Dose (mg/kg)						
Male	5.0	10.0	20.0	25.0	30.0	35.0	50.0
Female	2.5	5.0	10.0	15.0	20.0	25.0	

The animals were observed for a period of 14 days. Necropsies were performed.

Results

LD_{50} (male) - 30.8 (29.0-32.8) mg/kg
LD_{50} (female) = 16.1 (15.0-17.2) mg/kg
Toxic Signs: muscular tremors, cramps, breathing disorders, salivation
Necropsy: unremarkable
TOX Category: I
Classification: Core-Minimum Data
1) body weights and food consumption were not determined daily.

b. Acute Intraperitoneal Toxicity

225 Wistar II albino rats, weighing 160-180g, were distributed into 8 groups of 15 males each and 7 groups of 15 females each and administered the test material, diluted in a distilled water-Cremophor EL mixture, by intraperitoneal injection, according to the following schedule:

	Dose (mg/kg)							
Male	2.5	5.0	10.0	12.5	15.0	17.5	20.0	25.0
Female	1.0	2.5	5.0	6.0	7.5	10.0	12.5	

The animals were observed for a period of 14 days. Necropsies were performed.

Results

LD_{50} (male) = 15.9 (13.9-17.7) mg/kg
LD_{50} (female) = 7.8 (7.2-8.6) mg/kg
Toxic Signs: muscular tremors, cramps, breathing disorders, salivation
Necropsy: unremarkable
Classification: Core Data

c. Acute Dermal Toxicity

Experiment #1:

HOL 0654 was applied in concentrated form to the clipped dorsal skin of 55 Wistar II rats, weighing 160-180g, according to the following schedule:

Sex	Dose (µl/kg)	No. of Animals
M,F	25	5,10
M,F	50	5,5
M,F	100	10,5
M	175	10
M	250	5

The contact time was 24 hours and the observation period was 14 days.

Results

LD_{50} (male) = 117.6 (88.2-146.7) µl/kg

LD_{50} (female) 25 µl/kg

Toxic Signs: signs typical of cholinesterase inhibition
TOX Category: I
Classification: Core-Minimum Data
1) body weights and food consumption were not determined daily; necropsies were not performed.

Experiment #2

HOL 0654 was emulsified in distilled water and Cremophor EL and the emulsion was applied to the clipped dorsal skin of Wistar II rats, weighing 160-180g, according to the following schedule:

Sex	Dose (mg/kg)	No. of Animals
F	5	5
F	10	5
M,F	25	5,10
F	35	10
M,F	50	5,5
M	75	10
M	100	10
M	125	10
M	150	10

The contact time was 24 hours and the observation period was 14 days.

Results

LD_{50} (male) = 97.9 (85.9-108.9) mg/kg

LD_{50} (female) = 29.5 (24.8-34.7) mg/kg

Toxic Signs: signs typical of cholinesterase inhibition
TOX Category: I
Classification: Core-Minimum Data
1) body weights and food consumption were not determined daily; necropsies were not performed.

c. Inhalation Toxicity

Experiment #1

60 Wistar II albino rats, weighing 160-180g, were divided into 3 groups of 10 male and 10 female animals each and exposed in a dynamic flow inhalation chamber to analytical concentrations of 0.018, 0.068 and 0.353 mg/L of HOL 0654, dissolved in a mixture of ethanol/Lutrol (1:1), for a period of 1 hour. The animals were observed for a period of 14 days.

Results

LC_{50} (male) $>$ 0.353 mg/L (no deaths occurred)

LC_{50} (female) $\simeq$ 0.353 mg/L

Toxic Signs: signs typical of cholinesterase inhibition, impairment of general health.
TOX Category: II
Classification: Core-Minimum Data
1) the study in conjunction with the 2nd study below meet Core standards.

Experiment #2

110 Wistar II rats, weighing 160-180g, were divided into 6 groups of 10 males each and 5 groups of 10 females each and were exposed in a dynamic flow inhalation chamber to HOL 0654, dissolved in a mixture of ethanol/Lutrol (1:1), for a period of 4 hours. The following exposure schedule was employed:

	Dose (mg/L)*					
Male	.0016	.0064	.0272	.0638	.131	.195
Female	.0016	.0064	.0272	.0638	.131	.195

*dosage was determined analytically

The animals were observed for a period of 14 days.

Results

LC_{t50} (male) > 0.195 mg/L t= 4 hours

LC_{t50} (female) ≈ 0.0638-0.131 mg/L

Toxic Signs: signs typical of cholinesterase inhibition, impairment of general health
TOX Category: II
Classification: Core-Minimum Data
1) the data presented in both inhalation studies strongly suggest that the LC_{50} is greater than .2 mg/L/hour yet is probably less than 2 mg/L/hour; necropsies were not performed.

28. SRA 12869 (ester chloride); Acute Toxicity Studies - (Bayer AG-Institut Für Toxikologie, Report #45225, 5/27/75, Acc #096657)

a. Oral Toxicity

135 male Wistar II rats, weighing 150-210g, were distributed into 9 groups of 15 animals each and administered 10, 25, 50, 100, 250, 500, 1000, 2500 and 5000 mg/kg of SRA 12869 (ester chloride), emulsified in a mixture of Cremophor and water, by gavage. The animals were kept under observation for a period of 14 days.

Results

LD_{50} > 5000 mg/kg (1/15 deaths occurred)

Toxic Signs: general impairment of health
TOX Category: IV
Classification: Core-Minimum Data
1) although the LD_{50} was not actually determined, the results of the study clearly indicate an LD_{50} in excess of 5 g/kg.

b. Dermal Toxicity

SRA 12869 (ester chloride) was qpplied in concentrated form at a dose of 1.0 ml/kg to the clipped dorsal skin of 5 male Wistar II rats, weighing 150-210g. The treated area was covered with a plaster cast. After 24 hours, the plaster cast was removed and the skin was washed with soap and water. The animals were observed for a period of 7 days.

Results

LD_{50} >1.0 ml/kg

Toxic Signs: general impairment of health; the treated area of the skin became swollen, hard and encrusted on the third day.

Classification: Supplementary Data

1) too few dose levels were employed; a higher dose level should have been tested.

c. Inhalation Toxicity

SRA 12869 (ester chloride) contained in a sintered wash bottle, was vaporized by continuously directing air through it (for 1 or 4 hours) at a temperature of 22°C. The vapors were directed into a 10 L inhalation chamber in which mice or rats were present. The following exposure schedule was employed:

Conc.(mg/l)	Species	Exposure Time	No. of Animals
0.167	mice	1	10
0.167	rats	1	5
0.1042	mice	4	10
0.1042	rats	4	5
0.2083	mice	4	10
0.2083	rats	4	5
0.417	mice	4	10
0.417	rats	4	5

The concentration was determine gravimetrically by weighing the wash bottle initially and at the end of the exposure. The animals were observed for a period of 14 days.

Results

LC_{50} (mice) $>$ 0.167 mg/L

LC_{t50} (mice) $>$ 0.417 mg/L for t=4 hours

LC_{50} (rats) $>$ 0.167 mg/L

LC_{t50} (rats) $\approx$ 0.417 mg/L for t = 4 hours

Toxic Signs: breathing difficulties
TOX Category: could not be determined definitively
Classification: Supplementary Data
1) the LC_{50} was not determined.

d. Eye and Skin Irritation Studies

Skin Irritation:

0.5 ml of SRA 12869 (ester chloride) was placed onto cellulose pads and applied to the hairless inside section of one ear of each of two rabbits for 1, 2 or 8 hours.

Results

The exposed area of skin was markedly red. The degree of redness was not influenced by the time of contact. Redness of the skin persisted for 5 to 7 days.

TOX Category: N/A
Classification: Supplementary Data
1) a grading system was not employed.

Eye Irritation:

0.1 ml of SRA 12869 (ester chloride) was placed into the conjunctival sac of the right eye of each of two rabbits.

Results

One hour after application the conjunctivae were seen to be markedly reddened and mildly swollen. The redness and chemosis gradually receded after 5 days.

TOX Category: N/A
Classification: Supplementary Data
1) the degree of irritation was not quantitated.

29. Toxicological Studies to Evaluated Phenamiphos for Acute Oral Toxicity when Administered Simultaneously with Fensulfothion, Isofenphos or Phoxim - (Bayer AG-Institut Für Toxikologie, Report #47933, 3/15/76, Acc #096657)

a. Acute Oral Toxicity of Individual Compounds

i) Phenamiphos

Male Wistar II rats, weighing 160-180g, were distributed into 5 groups of 15 animals each and administered 2.5, 5, 7.5, 10 and 12.5 mg/kg of phenamiphos, emulsified in distilled water and Cremophor EL, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 7.3 (6.1-8.8) mg/kg slope = 1.29

ii) Fensulfothion

Male Wistar II rats, weighing 160-180g, were distributed 8 groups of 15 animals each and administered 1, 2.5, 5, 7.5, 8.5, 10, 12.5 and 15 mg/kg of the fensulfothion, emulsified in distilled water and Cremophor EL, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 10.0 (9.0-11.0) mg/kg slope = 1.15

iii) Isofenphos

Male Wistar II rats, weighing 160-180g, were distributed into 7 groups of 15 animals each and administered 10, 25, 30, 35, 45, 50 and 75 mg/kg of the test material, emulsified in distilled water and Cremophor EL, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 40 (36-44) mg/kg slope = 1.23

iv) Phoxim

Male Wistar II rats, weighing 160-180g, were distributed into 9 groups of 15 animals each and administered 100, 250, 500, 1000, 1750, 2500, 3500, 5000 and 7500 mg/kg of the Phoxim, emulsified in distilled water and Cremophor, by gavage. The animals were observed for 14 days.

Results

LD_{50} = 2825 (2325-3432) mg/kg slope = 1.47

b. Potentiation Studies

i) Phenamiphos & Fensulfothion

Male Wistar II rats, weighing 160-180g, were distributed into 5 groups of 15 animals each and administered 2.5, 5, 7.5, 10 and 15 mg/kg of an equitoxic mixture of phenamiphos and fensulfothion (emulsified in distilled water and Cremophor EL), by gavage. The animals were observed for 14 days.

Results

LD_{50} (observed) = 7.04 mg/kg

LD_{50} (experted) = 8.62 mg/kg

Potentiation was not produced.

ii) Phenamiphos & Isofenphos

Male Wistar II rats, weighing 160-180g, were distributed into 5 groups of 15 animals each and administered 10, 20, 25, 30 and 50 mg/kg of an equitoxic mixture of phenamiphos and isofenphos (emulsified in distilled water and Cremophor EL), by gavage. The animals were observed for 14 days.

Results

LD_{50} (observed) = 26.3 mg/kg

LD_{50} (expected) = 23.81 mg/kg

Potentiation was not produced.

iii) Phenamiphos & Phoxim

Male Wistar II rats, weighing 160-180g, were distributed into 6 groups of 15 animals each and administered 750, 1000, 2000, 2500, 3500 and 5000 mg/kg of an equitoxic mixture of phenamiphos and phoxim (emulsified in distilled

water and Cremophor EL), by gavage. The animals were observed for 14 days.

Results

LD_{50} (observed) = 2485 mg/kg Potentiation was not produced.

LD_{50} (expected) = 1250 mg/kg

Classification = Core Data

30. Acute Oral Toxicities of Some Oftanol Metabolites - Oftanol Oxygen Analog; Des N-Isopropyl Oftanol Oxygen Analog; Des N-Isopropyl Oftanol - (Chemagro R&D, Report #53884, 11/11/77, Acc #096657)

a. Oftanol Oxygen Analog

80 Holtzman Sprague-Dawley rats were distributed into 4 groups of 10 females each and 4 groups of 10 males each. The male rats were administered 14, 24, 41 and 70 mg/kg of the test material by gavage. The female rats were administered 5, 10, 20 at 40 mg/kg of the test material. The animals were observed for 14 days for signs of toxicity and mortality. Body weights were recorded on days 0, 7 and 15. Necropsies were performed.

Results

LD_{50} (male) = 38 (31-48) mg/kg

LD_{50} (female) = 17 (14-22) mg/kg

Toxic Signs: diarrhea, muscular fasciculations, tremors, lacrimation, lethargy, ataxia, convulsions, and rough hair coats.
Necropsy: congested lungs and livers; mottled kidneys.
TOX Category: I
Classification: Core-Minimum Data
1) food consumption and body weights were not determined weekly.

b. Des N-Isopropyl Oftanol Oxygen Analog

80 Holtzman Sprague-Dawley rats were distributed into 4 groups of 10 females each at 4 groups of 10 males each. The male rats received 41, 70, 118, and 201 mg/kg of the test material by gavage. The female rats received 29, 40, 57 and 80 mg/kg

of the test material. Body weights were recorded on days 0, 7 and 14. The animals were observed for 14 days. Necropsies were performed.

Results

LD_{50} (male) = 86 (69-108) mg/kg

LD_{50} (female) = 50 (44-56) mg/kg

Toxic Signs: diarrhea, muscular fasciculations, tremors, lacrimation, lethargy, ataxia, convulsions and rough hair coats.
Necropsy: congested lungs and livers; mottled kidneys
TOX Category: II
Classification: Core-Minimum Data
1) food consumption and body weights were not determined weekly.

c. Des N-Isopropyl Oftanol

80 Holtzman Sprague-Dawley rats were distributed into 4 groups of 10 males each and 4 groups of 10 females each. The male rats received 41, 70, 118 and 201 mg/kg of the test material, by gavage. The female rats received 111, 155, 218 and 305 mg/kg of the test material. The animals were observed for 14 days. Body weights were determined on days 0, 7 and 14. Necropsies were performed.

Results

LD_{50} (male) = 111 (83-148) mg/kg

LD_{50} (female) = 194 (155-244) mg/kg

Toxic Signs: diarrhea, muscular fasciculations, tremors, lacrimation, lethargy, ataxia, convulsions and rough coats.
Necropsy: congested lungs and livers; mottled kidneys
TOX Category: II
Classification: Core-Minimum Data
1) food consumption and body weights were not determined daily.

b. Evaluation of (P) ADI

1. Prior Tolerances

NA

2. (P) ADI Calculation

The (P) ADI is based upon erythrocyte cholinesterase inhibition observed in the 90-Day Dog Feeding study in which the NOEL = 1.0 ppm (0.025 mg/kg/day). With the imposition of a 200-fold safety factor* the (P) ADI is calculated to be:

$$0.025 \text{ mg/kg/day} \times \frac{1}{200} = 0.000125 \text{ mg/kg/day} = \text{(P) ADI}$$

*The 200 fold safety factor is derived as follows:

10X - for NOEL based on cholinesterase inhibition
times 20X - for extrapolation from a 90 day study to a 2 year study.

3. Impact of New Tolerances - (see attachment #3)

The maximum permissible intake (MPI) is 0.0075 mg/day for a 60 kg adult. If the temporary tolerance is established, the maximum theoretical residue contributed (MTRC) to the diet would be 0.0038 mg/day in the human 1.5 kg/day diet. This would account for 50.49% of the (P) ADI.

The (P) ADI will not be exceeded by establishment of this temporary tolerance on corn.

c. RPAR Criteria

The supporting toxicity data do not indicate that any RPAR criteria have been exceeded.

d. Discussion

SRA 12869 is an organophosphate compound. Its major mode of action is its ability to inhibit cholinesterase. It is highly toxic by the oral and dermal routes of exposure. Atropine in combination with obidoxime affords the greatest protection from the acute effects of the compound.

In subchronic oral experiments in dogs and rats, dogs appear to be slightly more sensitive to the cholinesterase inhibiting properties of SRA 12869. In rats the NOEL's for plasma, erythrocyte and

brain cholinesterase inhibition are 5 ppm. In dogs the NOEL's for plasma and erythrocyte cholinesterase inhibition are 0.3 and 1.0 ppm. Cholinesterase and minor body weight gain depression were the only effects observed in the repeated dosage studies.

SRA 12869 was shown not to be mutagenic in the Ames test and in the Dominant Lethal test. The compound was shown not to be teratogenic in rats and rabbits. When tested in hens for possible neurotoxicity, the compound gave a negative response. The compound was shown not to illicit sensitization in male guinea pigs when injected intradermally. Potentiation was produced when an equitoxic mixture of malathion and SRA 12869 was administered to rats. Potentiation was not produced when SRA 12869 was administered in combination with EPN, or with phenamiphos.

e. Conclusions

1. The submitted toxicity data will support the requested temporary tolerance of 0.1 ppm in or on corn; however, TOX defers to CB the question as to the appropriateness of the requested exemption from a tolerance. In addition, the question as to the disposition of the corn forage and whether or not finite residues are likely to occur should be addressed.

2. Sufficient toxicity data is available on the 3 formulations (Oftanol 6 Emulsifiable, Oftanol 15% Granular, Oftanol 20%* Granular) to permit their use under the experimental program provided the necessary labeling changes, as detailed in the recommendation section of the review, are incorporated into the 3 labels.

   *At the time registration is sought acute toxicity data on Oftanol 20% will be required.

3. The establishment of the temporary tolerance will not theoretically exceed the ADI.

   (see the recommendation section for future data requirements)

Attachments
R/D Init: GEWhitmore 4/15/78
WG/ccw 5/9/78

E for GEW 5/12/78